UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/760,362	01/12/2001	James C. Chen	25886-0062	1582

24961 7590 02/25/2003

HELLER EHRMAN WHITE & MCAULIFFE LLP
4350 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122-1246

EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	17

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/760,362	CHEN, JAMES C.
	Examiner	Art Unit
	" Neon" Phuong Huynh	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/26/01; 3/11/02; 9/27/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *7-10,13-15,25-35 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11,12,16-24 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s): 5, 7, 13, 17

4) ☐ Other

Application/Control Number: 09/760,362

Art Unit: 1644

DETAILED ACTION

1. Claims 1-37 are pending.

2. Applicant's election with traverse of Group XVI, Claims 1-4, 6, 11-12, 16-24 and 36 (now claims 1-6, 11-12, 16-24 and 36) drawn to a method to treat neovascular disease of the eye wherein the disease is macular degeneration that read on the specific photosensitizer chlorin and the specific antibody to VEGF receptor, filed 9/27/02, is acknowledged. The traversal is on the grounds that (1) Groups I-XXIV (herein Group 1), among groups XXV-XXXII (herein Group 2) and among Groups XXXIII-XL (herein Group 3) are not independent or distinct. (2) the election of species with respect to the photosensitizer is not correct. (3) claim 13 belongs to Group XVI because the method of claim 11 which recites that the second component of the bindable pair is selected from the group consisting of receptor. The VEGF receptor, which is part of the elected species, presents on the abnormal endothelium. (4) Group 1 is directed to a method for treating neovascular disease of the eye by administering a targeted photosensitizing compound that selectively binds to abnormal endothelium that lines or composes neovascular tissue and the neovascularization or proliferative angiogenesis is the process of new blood vessels form. These processes are generally associated with abnormal conditions such as the ocular disease associated with diabetic retinopathies, glaucoma, ARMD, and neovascular associated with tumors. The targeting is effected using agents that cause the photosensitizing compounds to be delivered to the endothelium and employ ligands that specifically bind to receptors that are expressed thereon. (5) Obvious type double patenting could not be asserted in the situation where the method to treat neovascular disease of the eye wherein the photosensitizer is chlorin linked to antibody to VEGF receptor and the disease is macular degeneration and (6) There is no burden on the Office to search all groups. Upon reconsideration, Group VIII, drawn to a method to treat neovascular disease of the eye wherein the disease is diabetic retinopathy that read on the specific photosensitizer chlorin and the specific antibody to VEGF receptor, has been rejoined with the elected Group XVI (now claims 1-6, 11-12, 16-24 and 36). Claim 13 will not be rejoin with the elected invention because claim 13 recites the **ligand** is selected from the group consisting of the ED-B domain of fibronectin, antibody specifically elicited to ED-B domain of fibronectin, [illegible] and $\alpha_v\beta_3$ integrin receptor and not the second component of the bindable

compound is bound to a first component, which the examiner interprets as the elected antibody that binds to the second component of the bindable pair, which is the VEGF receptor. In short, claim 13 does not recite the elected species such as antibody that binds to VEGFR. With regard to rejoining Groups I-XXIV (herein Group 1), among groups XXV-XXXII (herein Group 2) and among Groups XXXIII-XL (herein Group 3) as proposed, a prior art search of one group will not encompassed another even though it appears that the groups are within the same class. Further, a method of treating neovasuclar disease of the eye versus the method of treating tumor using specific targeting agents that differ with respect to their binding specificity are patentably distinct. It is a burden to search more than one invention. Therefore, the requirement of Group XVI (now claims 1-6, 11-12, 16-24 and 36) and Groups I-VII, IX-XV, XVII-XL is still deemed proper and is therefore made FINAL.

3. Claims 7-10, 13-15, 25-35 and 37 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-6, 11-12, 16-24 and 36 drawn to a method to treat neovascular disease of the eye wherein the disease is macular degeneration and diabetic retinopathy that read on the specific photosensitizer chlorin and the specific antibody to VEGF receptor are being acted upon in this Office Action.

5. The references A-DZ cited on PTO 1449 filed 4/2/02 have been crossed out because none of the cited references have been submitted to the Office.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 11-12, 16-24 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method to treat neovascular disease of the eye comprising administering a targeted photosensitizing compound such as verteporfin conjugated to [illegible] of fibronectin, benzoporphyrin conjugated to VEGF

illuminating the neovasculature tissue with light for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue but without impairing or destroying other tissue, **does not** reasonably provide enablement for (1) a method to treat any neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue as recited in claim 1, (2) the said method wherein said light is non-laser light, laser light, light emitting diode, or ambient light, (3) the said method wherein the treated neovascular disease is macular degeneration, or diabetic retinopathy, (4) the said method wherein the targeted photosensitizing compound is bound to *any* first component of *any* bindable pair and wherein *any* second component of *any* bindable pair is selected from the group consisting of *any* receptor present on abnormal endothelium, *any* ligand bindable to *any* receptor present on abnormal endothelium, *any* antigen present on abnormal endothelium, and *any* antibody bindable to *any* antigen on abnormal endothelium, (5) the method wherein the targeted photosensitizing compound is bound to any first component of any bindable pair and wherein any second component of any bindable pair is selected from the group consisting of *any* receptor present on abnormal endothelium, *any* ligand bindable to *any* receptor present on abnormal endothelium, any antigen present on abnormal endothelium, and *any* antibody bindable to *any* antigen on abnormal endothelium wherein the targeted photosensitizing compound is incorporated into a liposomal preparation, (6) a method to treat any neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue as recited in claim 1 wherein the targeted photosensitizing compound is bound to *any* bi-specific antibody construct that further comprises both *any* ligand component and any receptor component, (7) the said method to treat neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue as recited in claim 1 wherein the targeted photosensitizing compound is bound to any bi-specific antibody construct that further comprises both any ligand component and any receptor component wherein the targeted photosensitizing compound is incorporated into a liposomal preparation, (8) the method to treat neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue wherein the photosensitized neovasculature is illuminated for

neovasculature tissue is treated with a total fluence of light irradiation from between about 240 j/cm2 to about 900 j/cm2 and (10) a method of instructing any person to treat any neovascular disease of the eye comprising instructing any person to conduct a method to treat neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue as recited in claim 1 for treating *any* benign tumor, malignant tumor or malignant uveal melanomas. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method to treat neovascular disease of the eye comprising administering a targeted photosensitizing compound such as verteporfin conjugated to L19 antibody that binds to the ED-B domain of fibronectin, benzoporphyrin conjugated to VEGF that selectively binds to abnormal endothelium that lines or composes neovasculature tissue that is presence in retina, choroids or both for treating diabetic retinopathy or macular degeneration.

The specification does not teach how to make and use *any* method mentioned above because there is insufficient guidance as to the structure much less about the function of *any* "targeted photosensitizing compound", *any* "photosensitizing compound" is bound to *any* "first component of *any* bindable pair" and wherein *any* "second component of *any* bindable pair" is selected from the group consisting of *any* "receptor" present on abnormal endothelium, *any* "ligand" bindable to *any* receptor present on abnormal endothelium, *any* "antigen" present on abnormal endothelium, and *any* "antibody" bindable to *any* "antigen" on abnormal endothelium for treating any neovascular disease of the eye. Not only the structure of the any photosensitizing compound is not enabled, it is not clear which antigen on the abnormal endothelium is being [illegible]. With regard to binding pair, not only the specific ligand or receptor is not disclosed.

undisclosed bindable pair because the term "component" could be as little as one amino acid or it could be as much as 100 amino acids.

Stryer *et al* teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages). In the absence of guidance as to the structure of the protein such as the antigen, the receptor, or the ligand, as well as specific component of said receptor and ligand, it is unpredictable which undisclosed antigen, receptor, ligand, and component of said receptor and component of said ligand would be effective for targeting any photosensitizing compound to the abnormal endothelium as a method for treating any disease.

With regard to antibody, because the specific antigen, receptor or ligand is not disclosed, the binding specificity of the antibody is questionable, in turn, and the targeted photosensitizing compound would bind specifically to the undisclosed antigen on the abnormal endothelium as a method to treat neovascular disease of the eye is not enabled.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed antigen, first component of any bindable pair and second component of any bindable pair such as receptor, ligand, antigen, and antibody to said ligand on the abnormal endothelium, it is unpredictable the binding specificity of any undisclosed antibody to any antigen, ligand, receptor, or antigen would be useful for targeting the photosensitizing compound to the abnormal endothelium as a method to treat any neovascular disease of the eye. Given the indefinite number of "photosensitizing compound", "antigen", "bindable pair" of any ligand or receptor, antibody to any ligand, antibody to any receptor and whether said undisclosed ligand, receptor, antigen are expressed on the neovasculature tissue or abnormal endothelium, it is unpredictable which undisclosed ligand, receptor, antigen, antibody to said ligand or receptor would be effective for targeting the photosensitizing compound to the abnormal endothelium as a method to treat neovascular disease of the eye.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

[illegible] 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 1-6, 11-12, 16-24 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method to treat any neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue as recited in claim 1, (2) the said method wherein said light is non-laser light, laser light, light emitting diode, or ambient light, (3) the said method wherein the treated neovascular disease is macular degeneration, or diabetic retinopathy, (4) the said method wherein the targeted photosensitizing compound is bound to *any* first component of *any* bindable pair and wherein *any* second component of *any* bindable pair is selected from the group consisting of *any* receptor present on abnormal endothelium, *any* ligand bindable to *any* receptor present on abnormal endothelium, *any* antigen present on abnormal endothelium, and *any* antibody bindable to *any* antigen on abnormal endothelium, (5) the method wherein the targeted photosensitizing compound is bound to any first component of any bindable pair and wherein any second component of any bindable pair is selected from the group consisting of *any* receptor present on abnormal endothelium, *any* ligand bindable to *any* receptor present on abnormal endothelium, any antigen present on abnormal endothelium, and *any* antibody bindable to *any* antigen on abnormal endothelium wherein the targeted photosensitizing compound is incorporated into a liposomal preparation, (6) a method to treat any neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue as recited in claim 1 wherein the targeted photosensitizing compound is bound to *any* bi-specific antibody construct that further comprises both *any* ligand component and any receptor component, (7) the said method to treat neovascular [illegible] comprising administering *any* targeted photosensitizing compound which

in claim 1 wherein the targeted photosensitizing compound is bound to any bi-specific antibody construct that further comprises both any ligand component and any receptor component wherein the targeted photosensitizing compound is incorporated into a liposomal preparation. (8) the method to treat neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue wherein the photosensitized neovasculature is illuminated for such as at least 4 minutes. 20 minutes. 1 hours or 24 hours. (9) the said method wherein the neovasculature tissue is treated with a total fluence of light irradiation from between about 240 j/cm2 to about 900 j/cm2 and (10) a method of instructing any person to treat any neovascular disease of the eye comprising instructing any person to conduct a method to treat neovascular disease of the eye comprising administering *any* targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue as recited in claim 1 for treating *any* benign tumor, malignant tumor or malignant uveal melanomas.

The specification discloses only a method to treat neovascular disease of the eye comprising administering a targeted photosensitizing compound such as verteporfin conjugated to L19 antibody that binds to the ED-B domain of fibronectin, benzoporphyrin conjugated to VEGF that selectively binds to abnormal endothelium that lines or composes neovasculature tissue that is presence in retina, choroids or both for treating diabetic retinopathy or macular degeneration.

With the exception of the specific ligand such as the ones recite in claim 13 for a method to treat neovascular disease of the eye, there is insufficient written description about the structure associated with function of *any* "targeted photosensitizing compound", *any* "photosensitizing compound", *any* "first component of *any* bindable pair", *any* "second component of *any* bindable pair", *any* "receptor" present on abnormal endothelium, *any* "ligand" bindable to *any* receptor present on abnormal endothelium, *any* "antigen" present on abnormal endothelium, and *any* "antibody" bindable to *any* "antigen" on abnormal endothelium without chemical structure or amino acid sequence. Further, the binding specificity of the antibody is inadequately described because the antigen to which the antibody binds is also not adequately described. Further, the specification discloses only one ligand such as ED-B domain of fibronectin, one specific binding pair such as VEGF that binds to the VEGF receptor, and one antibody that binds to the ED-B domain of fibronectin for targeting only two photosensitizing compound such as verteporfin, and [illegible] of skill in the art would reasonably conclude that the disclosure fails to

possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1, 11 and 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "non-laser light source" in claims 23-24 has no antecedent basis in base claim 1 because the word "non-laser" is not recited in claim 1.

The recitation of "component" in claim 11 is ambiguous and indefinite because the specification does not define the specific component of any bindable pair. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 3, 4, 6, 18-22, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,756,541 (May 1998; PTO 1449).

The '541 patent teaches a method to treat neovasuclar disease of the eye such as age-related macular degeneration comprising administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular). The reference method [illegible] tissue with laser light for a period of

destroying other tissue (See column 5, lines 10-12 and lines 21, claims of '541 patent, in particular). The reference method wherein the reference targeted photosensitizing compound is formulated in liposome since it selectively delivers the reference compound to the low-density lipoprotein component of the plasma of neovascular tissue (See column 3, lines 40-45, in particular). The reference method wherein the photosensitizing compound is illuminated for about 1 minutes to about 2 hours, and more preferably at least 10-25 minutes (See column 5, lines 2-4, in particular). The reference irradiance varies from about 150 to 900 mW/cm2 or a fluence of 50 to 150 j/cm2 (See column 5, lines 47-48, in particular). Claim 36 is included in this rejection because the instruction to a person to conduct the claimed method at the time the invention was made is within the teachings of the '541 patent. Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 2, and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (May 1998; PTO 1449) in view of Boulton *et al* (Br J Opthlalmol 82: 561-568, 1998; PTO 892), Blaauwgeers *et al* (Am J Pathology 155(2): 421-428, 1999; PTO 892), Klyashchitsky *et al* (J of Controlled Release 29(1-2): 16-16, 1994; PTO 892) and Prewett *et al* (Cancer Res 59:

The teachings of the '541 patent have been discussed supra. The '541 patent further teaches the targeted photosensitizing compound is formulated in liposome since it selectively delivers the reference compound to the low-density lipoprotein component of the plasma of neovascular tissue (See column 3, lines 40-45, in particular).

The claimed invention in claim 2 differs from the teachings of the reference only that the method wherein the light is non-laser light.

The claimed invention in claim 11 differs from the teachings of the reference only that the targeted photosensitizing compound is bound to a first component of a bindable pair such as VEGF receptor antibody and wherein a second component of the bindable pair is VEGF present on abnormal endothelium.

The claimed invention in claim 12 differs from the teachings of the reference only that the targeted photosensitizing compound is incorporated into a liposomal preparation.

Boulton *et al* teach VEGF plays a role in neovascularization in diabetic retinopathy and antibody to VEGF detects VEGF in endothelial cell in the retinal or choroidal of diabetic retina (see Abstract, Table 1, page 563, column 1, first paragraph, in particular). Boulton *et al* teach VEGF binds to VEGF receptors on endothelial cells such as inner retina (See page 566, column 2, first full paragraph, in particular).

Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriocapillaris (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Blaauwgeers *et al* teach that unregulated VEGF secretion by RPE plays a role in neovascularization.

Klyashchitsky *et al* teach photodynamic therapy (PDT) is based on the ability of porphyrins and other photosensitizers to be accumulated preferentially in cells such as tumors and to generate singlet oxygen when activated by visible light (See abstract, in particular). Klyashchitsky *et al* further teach that targeting molecule such as antibody that is specific for antigen or the receptor is efficient and useful for delivery of PDT selectively to the tumor cells (See abstract, in particular).

Prewett *et al* teach antibody such as DC101 that binds specifically to Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document,

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody as taught by the '541 patent for the antibody to the VEGF receptor as taught by Prewett *et al* to target the photosensitizing compound such as chlorine and green porphyrin as taught by the '541 patent and Klyashchitsky *et al* to the neovascular tissue of the retina as taught by Boulton *et al* and Blaauwgeers *et al* for a method to treat neoavascular disease of the eye as taught by the '541 patent. Boulton *et al*, Blaauwgeers *et al* and Prewett *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klyashchitsky *et al* teach that targeting molecule such as antibody that is specific for antigen or receptor is efficient and useful for selective delivery of PDT to the site of interest (See abstract, in particular). Prewett *et al* teach antibody such as DC101 that binds specifically to the Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular). Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriocapillaris (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Boulton *et al* teach that VEGF binds to VEGF receptors on endothelial cells such as inner retina play a role in neovascularization in diabetic retinopathy (See page 566, column 2, first full paragraph, abstract, in particular). The '541 patent teaches that administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) is useful for treating neovasuclar disease of the eye such as age-related macular degeneration (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular).

16. Claims 1 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (May 1998; PTO 1449) in view of US Pat 6,051,230 (April 2000, PTO 892).

The teachings of the '541 patent have been discussed supra. The '541 patent further [illegible] compound is formulated in liposome since it selectively

delivers the reference compound to the low-density lipoprotein component of the plasma of neovascular tissue (See column 3, lines 40-45, in particular).

The claimed invention in claim 16 differs from the teachings of the reference only that the method wherein the targeting photosensitizing compound is bound to a bi-specific antibody construct that further comprises both a ligand component and a receptor component.

The claimed invention in claim 17 differs from the teachings of the reference only that the method wherein the targeted photosensitizing compound is incorporated into a liposomal preparation.

The '230 patent teaches various antibodies that bind specifically to VEGF (See column 83, lines 39-67 and column 84, Table X, in particular), various bispecific antibodies as well as a method of making various bispecific antibodies that comprise two chosen antibodies one desired such as VEGF receptor and a ligand component such as VEGF for targeting to endothelial cells of vascularization (See column 29, lines 20-42, claim 46 of '230 patent, in particular). The '230 patent teaches that bispecific antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature through recognition of VEGF and/or through receptor binding on endothelial cells (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody as taught by the '541 patent for the bispecific antibody that binds to the VEGF and the VEGF receptor as taught by the '230 patent for targeting the photosensitizing compound such as chlorine and green porphyrin as taught by the '541 patent to the neovasculature tissue for treating neovascular disease of the eye. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '230 patent teaches bispecific antibodies carrying diagnostic or therapeutic agents are targeted to the vasculature through recognition of VEGF and/or through receptor binding on endothelial cells (See abstract, in particular).

17. Claims 1 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (May 1998; PTO 1449) in view of US Pat 5,912,257 (June 1999, PTO 892).

[illegible] of the '541 patent have been discussed supra.

The claimed invention as recited in claim 23 differs from the teachings of the reference only that the method wherein the non-laser light source is a light emitting diode.

The claimed invention as recited in claim 16 differs from the teachings of the reference only that the method wherein the non-laser light source is ambient light.

The '257 patent teaches photosensitizing compound such as two-photon upconverting dye such as styryl compound that absorbs photon and fluoresces (See column 41, lines 12-15, in particular). The reference method wherein the detection can be detected by evaluating the intensity of emitted visible light such as ambient light (See column 38, lie 59-61, in reticular). The reference method wherein the light source can be incoherent light source, which is non-laser light source such as In GaAs diode (See column 37, lines 64-66, column 38, line 7, in particular). The reference photosensitizing compound is useful when light-induced singlet oxygen in photodynamic therapy to produce a cytotoxic effect on the cells (see column 13, lines 11-14, column 12, lines 44-65, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the photosensitizing compound such as chlorine and green porphyrin as taught by the '541 patent for the photosensitizing compound such as styryl compound as taught by the '257 patent for a method to treat neovascular disease of the eye as taught by the '541 patent that use non-laser light source. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '257 patent teaches that the reference photosensitizing compound is useful when light-induced singlet oxygen in photodynamic therapy to produce a cytotoxic effect on the cells (see column 13, lines 11-14, column 12, lines 44-65, in particular).

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be [illegible] examiner's voice mail service. If attempts to reach the examiner by telephone are

inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

February 24, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600